REMARKS AND ARGUMENTS

Claims 46-49, 51-52, and 64-67 are currently pending in the application. Claims 1-45, 50, and 53-63 have been previously canceled without prejudice to future filing. The pending claims are listed above in the listing of the claims, and are not amended at this time.

Applicants appreciate the withdrawal of the previous rejections of claims 46-49, 51-52, and 64-67 on the basis of 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103(a)

Claims 46-49, and 51-52 remain rejected, and claims 64-67 are currently rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. published application 2004/0028687 to Waelti, and publication of Yndestad et al. (*Cardiovasc. Res.* 2002 April, 54(1):175-82), in view of U.S. Patent 5,674,704 to Goodwin et al. This rejection is respectfully traversed.

35 U.S.C. § 103(a) states that "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

For all of the reasons set forth in the previous Response and Amendment of November 13, 2009, as well as previously submitted responses (March 18, 2009, and the Response of May 14, 2008), Applicants maintain that the subject matter of claims 46-49, 51-52, and 64-67 would not have been obvious to a person having ordinary skill in the art at the time the invention was made over Waelti and Yndestad et al. in view of U.S. Patent 5674704 to Goodwin et al.

First, Applicants appreciate the clarification from the Examiner regarding the Waelti published patent application, as qualifying as a prior art reference based on the effective filing date of the patent application, and understand the clarification.

Regarding the reference to Yndestad et al., however, Applicants maintain that the claimed subject matter would not have been obvious over this reference in combination with the

other references. The pending claims recite a method for reducing chronic cardiotoxicity caused by a chemotherapeutic agent in a subject in need of such a treatment comprising administering to the subject a 4-1BB antagonist, wherein the 4-1BB antagonist is selected from a soluble 4-1BB protein that blocks or reduces the interaction of 4-1BB and 4-1BB-L, an antibody that specifically binds 4-1BB and blocks or reduces the interaction of 4-1BB and 4-1BB-L, and an antibody that specifically binds 4-1BB-L and blocks or reduces the interaction of 4-1BB and 4-1BB-L.

First, as stated previously, Yndestad et al. found that 4-1BBL was one of *34* upregulated genes found in the peripheral blood mononuclear cells (PBMC) from chronic heart failure patients but not healthy blood donors (abstract page 175). Applicants submit, however, that it would not have been obvious from this reference that antagonizing 4-1BB *in particular*, and 4-1BB *alone*, would provide a reduction of chronic cardiotoxicity caused by a chemotherapeutic agent, for the following reasons.

First, the study described in Yndestad et al. did not result in the identification of any single factor correlating to chronic heart failure, but instead indentified the plurality of factors associated with this condition. As the authors stated, "the objective of the study was to characterize the *imbalance* in the cytokine *network* in CHF (chronic heart failure)" (abstract page 175, emphasis added).

Second, according to Ynedstad et al., although 4-1BBL was one of the 34 upregulated genes, 4-1BBL was not considered to be "significantly upregulated". As stated on page 175, (abstract) "quantitative RT-PCR confirmed significantly upregulated gene expression of APRIL, LIGHT, FasL and CD27L" (page 175, abstract) (but *not* 4-1BBL) in CHF patents.

The Examiner has taken the position that the fact that the upregulation of 4-1BBL could not be confirmed using RT-PCR does not amount to "teaching away" from "the selection of 4-1BBL as the target to antagonize" (page 3, Office Action of 2/17/2010) but merely points to the "technical difficulty" of RT-PCR due to "low hybridization signals" of both 4-1BBL and CD40L. However, this position is not consistent with what is presented in Ynedstad et al. For example in the Discussion section, 4.1 (page 179, second column, second paragraph), the authors stated "we have pinpointed several potentially interesting genes and gene families in the cytokine network that should be further investigated for their possible pathogenic role in this disorder. In

particular, we found a marked upregulation of several ligands in the TNF superfamily as demonstrated by ***both*** cDNA expression arrays ***and*** real-time quantitative RT-PCR methods." (emphasis added). Clearly, the authors *do* attach significance to the fact that the upregulation of 4-1BBL and CD40L "were not verified" by RT-PCR (page 180, first column, first paragraph). Thus the low hybridization signals related to low abundance of transcripts for 4-1BBL and CD40L did not merely mean technical difficultly, but clearly was interpreted as being less significant than the "marked upregulation" of other TNF ligands.

Third, as stated previously, the authors noted that "receptors for APRIL, FasL, LIGHT, TNFα, and TRAIL have been reported to be expressed in the heart" (page 180, section 4.3) but *not* 4-1BB. Further, no mention is made of 4-1BB or 4-1BBL in the discussion of potential pathological implications, section 4.3, pages 180-181, although other TNF superfamily ligands are discussed.

Thus, for these reasons, as well as the reasons previously presented, Applicants maintain that it would not be obvious to identify 4-1BB or 4-1BBL *in particular* as a target to antagonize as a treatment for chronic cardiotoxicity caused by a chemotherapeutic agent based on the reference to Ynedstad et al., in combination with the other cited references.

Therefore, based on the arguments presented above, as well as the arguments previously presented, Applicants request reconsideration and withdrawal of the rejection of claims 46-49, 51-52, and 64-67 on the basis of 35 U.S.C. §103(a) as allegedly unpatentable over the publication of Yndestad et al., and U.S. application 2004/0028687 to Waelti, in view of U.S. Patent 5,674,704 to Goodwin et al.

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CONCLUSION

Applicants maintain that the claims as set forth are in form for allowance. Applicant's attorney invites the Examiner to call her at the number given below if it would be helpful in advancing the prosecution of this application.

Respectfully submitted,

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